

Applying Density Functional Theory to Common Organic Mechanisms: A Computational Exercise

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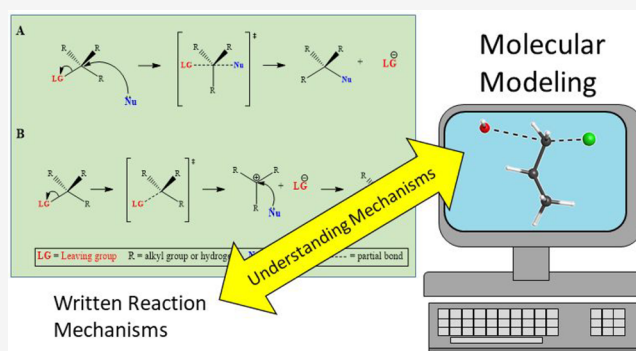
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ABSTRACT: A computational experiment investigating common organic chemistry mechanisms has been developed and implemented in a junior/senior-level physical chemistry laboratory course at two institutions. Students investigated various reactions that proceed via S_N1 , S_N2 , E1, and E2 mechanisms using hybrid Density Functional Theory (DFT). Our pre/post-assessments indicate that students at both institutions were able to better visualize and interpret the 3D representation of transition states, stepwise reaction mechanisms, and reaction coordinate diagrams of the aforementioned reactions.

KEYWORDS: Third-Year Undergraduate, Fourth-Year Undergraduate, Organic Chemistry, Physical Chemistry, Computer-Based Learning, Computational Chemistry, Mechanisms of Reactions, Quantum Chemistry



INTRODUCTION

The integration of theory, computations, and experiments is essential in preparing students for future careers in science. This is epitomized by the “Materials Genome Initiative,” a federal multiagency initiative that promotes the integration of computational and experimental tools with digital data to develop materials in an integrated paradigm that is significantly faster and less costly than the traditional trial-and-error laboratory approach.¹ To educate and train the future generation materials research and development workforce, students must be exposed to computational modeling in their undergraduate education. In an effort to introduce computational chemistry into the traditional undergraduate chemistry curriculum, a number of computational chemistry laboratory exercises have been developed and implemented in this *Journal*, which are associated with organic chemistry.^{2–14} Herein, we add to the library of computational exercises one that investigates common organic reactions that are studied primarily in organic chemistry courses. This set of exercises is appropriate for both a lecture-based sophomore organic chemistry course and a junior/senior physical chemistry laboratory exercise.

A major hurdle/barrier for students (and instructors) to overcome is the time it takes to recognize the meaning, importance, and relevance of organic structures and mechanisms; for many students the entire subject of organic chemistry will remain an abstract construct well into

adulthood.^{15–17} Visualization is quite important for interpreting key factors in chemistry, which can lead to improved acquisition and retention of different concepts.^{18–21} We have found that development through computational exercises can be beneficial to student understanding at various stages in one’s chemical education because computational chemistry naturally enables visualization of molecules and reactions.^{22–26}

Traditionally, some of the first mechanisms introduced in organic chemistry are substitution and elimination reactions. These reactions fall into four categories: S_N1 , S_N2 , E1, and E2. It has been found that students usually struggle in visualizing and predicting the pathway of these reaction mechanisms.²⁷ The difficulty students have in predicting the mechanistic details has been attributed to the interplay of steric and electronic effects on the mechanisms themselves.²⁸ To help students better understand reaction mechanisms organic chemistry instructors around the world have focused on teaching how to predict products by considering the stability of the leaving groups or the nucleophile strength.^{27–30} This

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activity focuses on the reaction coordinates and thermodynamics of different mechanisms to help students predict the likelihood of each reaction.

The reaction coordinate is a topic that is covered to a great extent in general chemistry courses. Forming a connection between the “classic knowledge” taught in general chemistry and the “new knowledge” in organic chemistry could be beneficial for information retention. Completing exercises that connect the two areas will also help to resolve any misconceptions students might have about reaction coordinates.³¹

Additionally, reaction coordinate diagrams can be constructed in a more quantitative way from the results of quantum chemical calculations. Many students lack exposure to these calculations outside of the qualitative illustrations in their textbook or lecture slides.³² To provide another avenue for quantum mechanical models to trickle into the undergraduate curriculum, herein we describe a computational exercise that aims to improve student visualization and interpretation of essential organic chemistry mechanisms.

■ EXPERIMENTAL OVERVIEW

The learning objectives of the experiment are as follows:

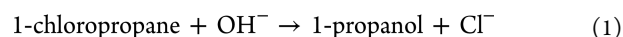
- Better comprehension of mechanisms common in organic chemistry using a visual graphic.
- Understand and prepare reaction coordinate diagrams based on quantum chemical calculations.
- Tabulate and interpret the energetics of a chemical reaction via quantum chemical calculations.
- Application of quantum chemical models to chemical reactions using guided assistance.
- Learn how to identify transition states computationally using vibrational frequency calculations.
- Explain how thermochemical data was obtained using first-principles molecular software.

This experiment was implemented at two separate institutions: St. Bonaventure University (SBU), a small private liberal arts institution, and the State University of New York, University at Buffalo (UB), a large public research institution. The experiment was performed in two 4-h/5-h long sessions at SBU/UB, respectively. Students could also access the computational software online, enabling students to work on the exercise from home. On the first day of the experiment, a short pre-exercise lecture was delivered to ensure students understood the basics required to complete the exercise, followed by a pre-exercise quiz. The 8 students who conducted the exercise at SBU were either junior or senior chemistry majors enrolled in the quantum portion of the physical chemistry sequence. All the students at SBU had completed/passed the thermodynamics portion of physical chemistry (CHEM 401: Physical Chemistry I). The 12 students at UB were junior and senior chemistry, medicinal chemistry, and biochemistry majors. Each student at UB had taken at least a single undergraduate physical chemistry class. While, for some students, this was the thermodynamic portion of the second semester physical chemistry sequence, others had completed a one-semester physical chemistry course for life science majors. Very few of the students had taken, or were simultaneously enrolled in, a physical chemistry class where quantum mechanics is introduced. Students had prior experience utilizing WebMO to build molecules, submit calculations, and analyze outputs. Specifically, students at SBU had

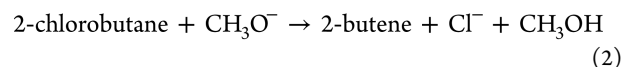
conducted 4 other exercises that used WebMO while students at UB had conducted 3 other exercises along with a tutorial.

The exercise consists of 3 sections where students investigate S_N2, S_N1, E2, and E1 reaction mechanisms. The reactions that were investigated were:

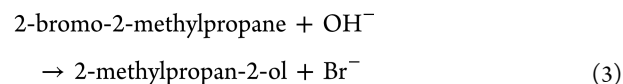
S_N2, Section 1:



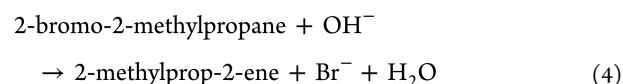
E2, Section 2:



S_N1, Section 3:



E1, Section 3:



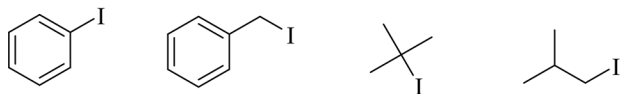
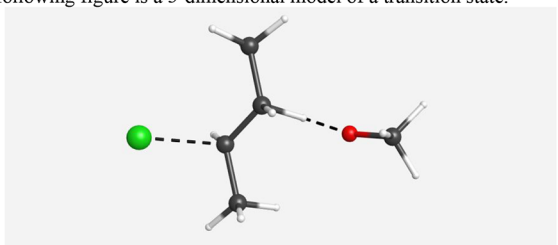
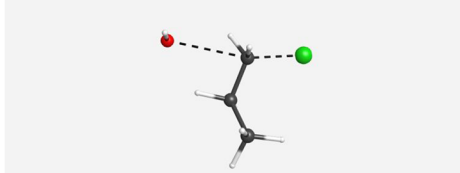
In section 1, students consider a S_N2 reaction of 1-chloropropane with hydroxide to make 1-propanol and a chlorine anion (eq 1). Students were tasked with determining changes in energy (ΔE), changes in the Gibbs Free Energy (ΔG), and the activation energy (E_A) for the previously mentioned reaction. Students visualized the imaginary frequency of the transition state for reaction 1 to see the backside attack commonly referenced in organic chemistry courses for the S_N2 mechanism. Students were also required to draw a reaction coordinate diagram based upon their calculated results (ΔG , E_A , etc.).

In section 2, an E2 reaction of 2-chlorobutane with a methoxy anion to produce 2-butene, a chlorine anion, and methanol was studied (eq 2). This section basically mirrored section 1, with the added complexity of identifying the *cis*- or *trans*-stereoisomers of butene's product and visualizing the transition state with the partial bonds breaking/forming, resulting in the E2 product.

In section 3, students predict if an S_N1 or E1 reaction will occur between 2-bromo-2-methylpropane and a hydroxide anion. The overall reactions can be seen in eqs 3 and 4. Students were asked to determine which reaction mechanism is thermodynamically favorable and which was kinetically favorable. It was determined that the S_N1 mechanism is unsurprisingly favored both kinetically and thermodynamically. While this exercise did not ask the students to consider the inherent error of their DFT calculations, and if the differences in energies were meaningful, it was suggested that students read “Predicting Molecules-More Realism, Please!” by Hoffmann, Schleyer, and Schaefer to better understand meaningful differences of theoretical results.³³ Additionally, another article in this *Journal*, which focuses on a computational investigation of a Diels–Alder cycloaddition, also briefly touches on the limits of accuracy when considering activation energies.² The authors are also aware that S_N1 mechanisms can result in a mixture of chiral products, when applicable. We have selected a product (2-methylpropan-2-ol) that is achiral. We leave it to the instructor to mention this aspect of S_N1 mechanisms.

The resulting thermodynamic values (ΔE , ΔG , and E_A) are contained in the “Notes for the Instructor,” and are reported in

Table 1. Assessment Questions and Pre-assessment/Post-assessment Responses

Assessment Tasks	Students' Correct Responses, %	
	Pre-assessment (N=20)	Post-assessment (N=19)
1. Draw the reaction coordinate diagram for a generalized S _N 2 reaction.	20.0 %	73.7 %
2. Draw the reaction coordinate diagram for a generalized E2 reaction.	20.0 %	73.7 %
3. Draw the reaction coordinate diagram for the core steps of the generalized S _N 1/E1 reactions.	20.0 %	68.4 %
4. Rank the following in order of leaving group ability (1 = best) $\ominus\text{NH}_2$ H_2O $\ominus\text{Cl}$ $\ominus\text{I}$	15.0 %	15.8 %
5. Rank the following in order of S _N 2 reactivity (1 = most reactive) 	5.0 %	5.3 %
6. The following figure is a 3-dimensional model of a transition state.  This is an example of the transition state for what type of mechanism: a) S_N1 b) S_N2 c) E1 d) E2 e) I don't know	30.0 %	68.4 %
7. The following figure is a 3-dimensional model of a transition state.  This is an example of the transition state for what type of mechanism: a) S_N1 b) S_N2 c) E1 d) E2 e) I don't know	30.0 %	89.5 %
8. Which is the most stable carbo-cation? a) CH ₃ ⁺ b) CH ₂ CH ₂ ⁺ c) CH(CH ₃) ₂ ⁺ d) C(CH ₃) ₃ ⁺ e) I don't know	75.0 %	78.9 %
9. Which is more likely to undergo an S _N 1 or E1 reaction? a) C(CH ₃) ₃ Cl b) C(CH ₃) ₃ F c) C(CH ₃) ₃ Br d) C(CH ₃) ₃ I e) I don't know	30.0 %	31.5 %
10. Given that the following reaction proceeds via an E2 mechanism, draw out the reaction mechanism. Include a structure for each intermediate and transition state if applicable: 2-chlorobutane + CH ₃ O ⁻ → 2-butene + Cl ⁻ + CH ₃ OH	25.0 %	73.7 %
11. Given the following reaction proceeds via an S _N 2 mechanism, draw out the reaction mechanism. Include a structure for each intermediate and transition state if applicable: 1-chloropropane + OH ⁻ → 1-propanol + Cl ⁻	25.0 %	78.9 %

kJ/mol as a more relatable unit to what is utilized in common organic chemistry textbooks. A link to a WebMO tutorial is included in the "Notes for Instructors" that is contained in the [Supporting Information](#) to help instructors/students run the calculations.

Materials Required

This exercise was conducted with the web-browser-based WebMO version 18.1 interfaced³⁴ to Gaussian 16 at SBU.³⁵ A

free version of WebMO is available; however, we elected to use the proprietary Enterprise Version to use the queueing system implemented on our computer clusters. The Beowulf computer cluster utilized in the experiment was equipped with 4 Dell PowerEdge R300 servers. These servers were equipped with 3.16 GHz quad-core processors and 16 GB of RAM.

At UB, this exercise was conducted with the WebMO version 21.0.010e and Gaussian 16. UB's computer cluster

utilized 4 nodes with two Intel Xeon E5-2430 CPUs (hexa-core with 12 threads) and 48 GB of RAM.

At each university, each student had their own computer/workstation to log onto each university's WebMO login page. Most geometry optimizations and vibrational frequency calculations took on the order of minutes/hours to complete.

HAZARDS

There are no physical hazards involved with this experiment.

RESULTS AND DISCUSSION

The resulting thermodynamic values (ΔE , ΔG , and E_A) and answers to the exercises are reported in the "Notes for the Instructor" contained in the [Supporting Information](#).

Student learning of content was assessed by a pre/post-test evaluation and a summative laboratory report prepared by the students.

The pretest was given before the start of the experiment, while the post-test was given at the end of the experiment. For both institutions, the postlab assessment was conducted 3 weeks after the start of the exercise. This was the same date that the laboratory report was due. Students showed growth over the course of the semester with an increase in the number of correct responses. [Table 1](#) indicates the questions that were asked, along with the correct number of student responses in both the pre/post-assessment. The full pre/post-assessment is contained in the [SI](#) for instructor use. This pre/post-assessment was utilized by both SBU and UB.

Questions 1, 2, 3, 6, 7, 10, and 11 were explored in the exercise, the laboratory manual, and in the prelaboratory lecture. The average improvement on these questions was approximately 50%. Questions 4, 5, 8, and 9 were not explicitly explored in the exercise, laboratory manual, or in the prelaboratory lecture allowing for these questions to be considered "control questions." These control questions resulted in a 5% improvement in the postassessment. These questions considered the reaction conditions/reagents for these different mechanisms. It is clear from this data that students did not gain a greater understanding of how reaction conditions change the proceeding mechanism but indicate a greater understanding in the topics covered by the exercise.

Question 8, a question about carbo-cation stability, had the highest correct response rate of all the questions in the preassessment. Assessment questions 6 and 7 are connected to the 3D visualization of the transition states for S_N1/S_N2 mechanisms. Most of the students were able to correctly identify the mechanism associated with the transition state in the post assessment, and a substantial improvement was made compared to the preassessment. Assessment questions 1–3 are connected to the thermodynamics of the reaction mechanisms. The correct student response rate increased by approximately 50% for each question. Assessment questions 10 and 11 asked the students to write out specific reaction mechanism steps, something that would be commonly asked in an organic chemistry course, for two reactions. These assessment questions showed improvement in student understanding, but these reactions are the specific reactions studied in the exercise. If a different reaction was considered, it is unclear if students could correctly determine the reaction mechanism.

The summative assessment of a written lab report indicated that 75% of students correctly determined that the reaction in section 3 of the exercise occurs via a S_N1 mechanism both

kinetically and thermodynamically. All the students at SBU and 7 of the 12 students at UB determined the correct mechanism for section 3. Those who reported the incorrect mechanism either calculated the reaction and activation energies incorrectly or the structures utilized in the calculation of the activation energy/change in Gibbs free energy were not ground states. It was observed that imposing symmetry constraints during geometry optimizations were the main reasons for the incorrect ground state geometries.

Generally, students did not find the modeling aspect of the exercise difficult but found the data analysis was challenging and more time-consuming than they had expected. Common problems associated with this exercise included:

- Conducting geometry optimization on the provided transition states.
- Failing to include an implicit solvation model in the calculations.
- Selecting the incorrect solvent for the implicit solvation model.
- Failure to visually inspect the optimized geometry to determine if the output geometry was correct. For example, some students constructed flat sp^3 carbon-containing molecules that optimized to planar geometries due to symmetry constraints.
- Failure to determine the geometry was a local minimum from the vibration frequency calculation.
- Incorrectly constructing then calculating geometries of reactants, products, and intermediates.
- Incorrectly assigning the proper charge/multiplicity of charged systems.
- Incorrectly calculating changes in energy/Gibbs free energy by omitting required thermodynamic data or incorrectly tabulating the data

Students became aware of issues with calculations when the changes in Gibbs free energies did not match their chemical intuition. Correction of these calculations was typically done via email interactions or one-on-one interactions with the instructor.

Additional topics that could be explored by instructors include:

- Investigations of different solvents.
- Investigation of different density functionals beyond B3LYP.
- Investigation of increasing/decreasing basis set size.
- Instruct students to calculate their own transition state geometries. It is *highly* suggested to only consider this optional exploration if there is sufficient time and if the instructor is willing to instruct students about the different methods (such as linear or quadratic transit methods) to obtain transition states.

This same exercise was conducted with GAMESS and Spartan, with similar results found to those obtained with Gaussian. However, the investigations utilizing GAMESS and Spartan were conducted by 2 students and 2 instructors. Therefore, Gaussian may not be the only software that could be used for this exercise. An open-source software package, such as ORCA³⁶ or NWChem,³⁷ may be selected for use. If computing power is limited, investigations on these reaction mechanisms in respect to Gibbs free energies and vibrational frequencies may not be an option, unless a lower level of theory (nonhybrid density functional, or smaller basis set) is utilized.

SUMMARY

Physical chemistry students at two independent universities, a primarily undergraduate university (PUI) and an R1 institution, conducted a computational exercise investigating common organic reaction mechanisms via density functional theory. Based on pre/post-assessment data, students improved in their abilities to identify 3D renderings of transition states, to understand reaction coordinate diagrams/thermodynamics of common organic mechanisms, and to write out stepwise reaction mechanisms.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemeduc.2c00935>.

Coordinates (PDF, DOCX)
Grading Rubric (PDF, DOCX)
Notes for Instructors (PDF, DOCX)
Student Assessment Instrument (PDF, DOC)
Prelab Quiz (PDF, DOCX)
Potential Energy Surface, Geometry Optimization and Frequencies Calculation (PDF, DOCX)
XYZ Files (ZIP)

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Notes

The authors declare no competing financial interest.

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